

REMARKS

The Official Action of May 27, 2007, and the references cited therein have been carefully considered. The Applicant respectfully requests reconsideration of the application in view of the following remarks. Claims 1-14 have been canceled without prejudice and rewritten for presentation as new Claims 15-27. Support for this amendment is found in the specification, e.g. pages 4-11, and the claims of the application as filed.

Claims 15-27 are pending in the application.

I. Rejection of Claims 1, 10, 13 and 14 for Anticipation by Dorn et al. (U.S. Patent No. 5,719,147)

Claims 1, 10, 13 and 14 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Dorn et al. (U.S. Patent No. 5,719,147). Applicants respectfully traverse this rejection and submit that Dorn et al. does not disclose each and every element of the claimed invention.

Example 75, column 104, of U.S. Patent No. 5,719,147 discloses processes for obtaining the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine from 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine [which corresponds to the compound of the formula 2 in Claim 15] by using the procedure of Example 17, column 102, wherein 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetylrazono)morpholine is prepared and is heated in xylenes at reflux for 2 hours.

Applicants note that the processes of Dorn et al. for obtaining the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine utilize e.g., the free base of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine. In contrast, the present claims employ the hydrochloride salt of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine. Thus, Dorn et al. does not disclose each and every element of the claimed invention.

Accordingly, the rejection of Claims 1, 10, 13 and 14 under 35 U.S.C. § 102(b) as being anticipated by Dorn et al. (U.S. Patent No. 5,719,147) is untenable and should be withdrawn.

II. Rejection of Claims 10-14 for Obviousness over Dorn et al. (U.S. Patent No. 5,719,147)

Claims 1-14 stand rejected under 35 U.S.C. § 103(a) as being obvious over Dorn et al. (U.S. Patent No. 5,719,147). The Applicants respectfully traverse this rejection and provide the following comments.

The Applicants respectfully assert that U.S. Patent No. 5,719,147 does not disclose or suggest the claimed invention. Nor would U.S. Patent No. 5,719,147 have motivated or enabled one skilled in the art to prepare the subject compounds in accordance with the claimed invention. The Examiner has failed to demonstrate the specific motivation in U.S. Patent No. 5,719,147 that would have motivated one of ordinary skill in the art to prepare and utilize the subject compound in accordance with the claimed invention. The Examiner has failed to establish a prima facie case of obviousness. Even if the Examiner has established a prima facie case of obviousness, the present invention provides unexpected results relative to the disclosure of U.S. Patent No. 5,719,147.

U.S. Patent No. 5,719,147 discloses at Example 75, column 104, processes for obtaining the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)-phenyl-4-(3-(5-oxo-1,2,4-triazolo)methylmorpholine starting from:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-morpholine, by using the procedure of Example 70, column 102, wherein:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine is reacted with:

N-methylcarboxy-2-chloro-acetamidrazone, and

N,N-diisopropylethylamine in acetonitrile at room temperature for 20 hours, to give:

2-(R)-(1-(R)-(3,5-bis(trifluoro-methyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(2-(N-methyl-carboxyacetamidrazono)morpholine, which is:

heated in xylenes at reflux for 2 hours.

The process disclosed in U.S. Patent No. 5,719,147 is very different from the presently claimed process.

As the Examiner notes, U.S. Patent No. 5,719,14 does not teach any of the following reaction conditions:

- (1) the temperature of the cyclization process;
- (2) the use of the hydrochloride salt of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholine;
- (3) the use of toluene;
- (4) the use of an inorganic base (such as potassium carbonate);
- (5) the use of a polar aprotic solvent (such as dimethylsulfoxide or dimethylformamide); or
- (6) the use of an aqueous wash, such as with an aqueous salt solution, prior to conducting the cyclization.

Applicants respectively submit that there would have been no motivation nor guidance in U.S. Patent No. 5,719,147 for one of ordinary skill in the art to have conducted the subject process in accordance with the claimed invention. The Examiner has not provided specific factual basis to support the assertion that U.S. Patent No. 5,719,147 would have motivated one of ordinary skill in the art to have conducted the subject process in accordance with the claimed invention

There would have been no motivation in U.S. Patent No. 5,719,147 to have conducted the cyclization process at a temperature of about 140-150°C in the absence of xylene. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the solvent xylene would have been required.

There would have been no motivation in U.S. Patent No. 5,719,147 to have used the hydrochloride salt of the compound 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)-phenyl)ethoxy)-3-(S)-(4-fluoro)phenylmorpholin. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by indicating that the free base of the compound should be employed. The process conditions disclosed in Example 101, column 131, are not relevant because the hydrochloride salt of the compound 2R-cis-3,5-bis-(trifluoromethyl)benzeneacetic acid 3-(4-fluorophenyl)-4-phenylmethyl)-2-morpholinyl ester was prepared so as to remove tri-sec-butyl borane residue (from L-Selectride reduction).

There would have been no motivation in U.S. Patent No. 5,719,147 to use toluene, rather than xylene. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the solvent xylene would have been required.

There would have been no motivation in U.S. Patent No. 5,719,147 to use an inorganic base, rather than the organic base N,N-diisopropylethylamine. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that N,N-diisopropylethylamine would have been required, particularly when using acetonitrile as a solvent. The process conditions disclosed in Example 83, column 107, are not relevant because they were employed to alkylate a morpholine starting material with a bromo-methyl imidazolone (rather than N-methylcarboxy-2-chloro-acetamidrazone).

There would have been no motivation in U.S. Patent No. 5,719,147 to use a polar aprotic solvent (such as dimethylsulfoxide or dimethylformamide), rather than acetonitrile. In fact, U.S. Patent No. 5,719,147 teaches away from the present invention by suggesting that the solvent acetonitrile would have been required.

Finally, there would have been no motivation in U.S. Patent No. 5,719,147 to use an aqueous wash, such as with an aqueous salt solution, prior to conducting the cyclization.

Even if one of ordinary skill in the art had been motivated to alter the process disclosed in U.S. Patent No. 5,719,147, there would have been no direction in U.S. Patent No. 5,719,147 regarding which specific reagents, solvents, temperature, additional steps and/or other conditions should have been employed in the process.

Accordingly, Applicants respectfully submit that the Examiner has failed to establish a prima facie case of obviousness.


Even if the Examiner has established a prima facie case of obviousness, the present invention provides unexpected results relative to the disclosure of U.S. Patent No. 5,719,147. As noted in the specification (page 1, lines 14-19), the present invention provides a more practical and economical method for preparing the desired compound. As noted in the specification (page 7, lines 12-13), the present invention further provides an efficient process for preparing the desired compound that also minimizes the use of toxic solvents. Surprisingly, the present invention also gives the desired compound in 85% yield (page 8, lines 8-9), which is unexpectedly higher than the yield disclosed for the procedure in U.S. Patent No. 5,719,147 (79% yield) (Example 75, column 104).

Accordingly, Applicants respectfully submit that the rejection of Claims 1-14 under 35 U.S.C. § 103(a) as being obviousness over Dorn et al. (U.S. Patent No. 5,719,147) is untenable and should be withdrawn.

Serial No.: 10/511,691
Case No.: 20974YP
Page 10

Applicants respectfully contend that the application is allowable and a favorable response from the Examiner is earnestly solicited.

Respectfully submitted,

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